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Valvular Disease

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The valvular disease highlights at the Scientific Session of the 2004 American College of Cardiology (ACC) national meeting were focused on newer therapies for mitral regurgitation (MR), a glimpse at the ongoing interest in percutaneous approaches to valve replacement, the improvement in outcomes of valvular surgery patients with poor left ventricular (LV) function, an update of our knowledge base for endocarditis, and a novel observation regarding functional tricuspid regurgitation (TR) in patients with pulmonary hypertension and a dilated LV.

Skeletal myoblast implantation into an area of myocardial infarction initially was thought to improve diastolic function more than systolic function (1). More recent studies have suggested regional systolic LV function may improve as well (2), and the concept has now been extended to human trials (3). Whether myoblast transplantation might not only improve regional ventricular function but also reduce abnormal mitral leaflet tethering and the severity of ischemic MR was addressed in a sheep model by Messas et al. (4) from Paris, France, and Boston. After inducing MR by creating an acute infero-basal myocardial infarction, three-dimensional echocardiography was used to visualize the LV chamber dimensions and mitral valve anatomy. Two months after recovery, the animals were randomized, with one-half receiving autologous skeletal myoblast implantations in multiple sites within the infarcted area. The animals were then re-imaged two months after the implantations. Animals that received myoblast implantation had less progression in their MR, less increase in their LV end-systolic volume, and less measurable tethering distance from the anterior annulus to the tip of the ischemic papillary muscle. In addition, the myoblast animals had a better overall ejection fraction (EF) and better wall motion scores on the follow-up study. These data raise the possibility of improving ischemic MR by use of such myoblast transplantation techniques.

Another novel approach to the problem of MR has been recent attempts at percutaneous mitral repair using catheter-based techniques. In general, these methods have involved the use of a crimping-type catheter placed in the coronary sinus to reduce the mitral annular size (5) or the creation of a double-orifice mitral valve by the transseptal delivery of a clip device that grasps the mitral leaflet edges (6). This latter method has undergone previous surgical trials with and without an accompanying surgical annuloplasty (7). Dr. Feldman presented the current status of the phase 1 U.S. trials on the edge-to-edge percutaneous technique. Of note, although there have been previous publications demonstrating that the surgical edge-to-edge mitral repair method does not induce a significant mitral gradient (8), Sportouch et al. (9) reported at these meetings that some resting and exercise mitral gradients can be demonstrated, and a moderate amount of cardiogenic exercise limitation was observed in one-third of patients. Percutaneous methods for reducing MR hold the potential for providing enormous benefit for patients with MR, especially those associated with cardiomyopathy, who might otherwise not be surgical candidates.

The interest in percutaneous approaches to aortic valve replacement also remains high, with several devices being investigated and reported in either the in vitro setting or in early animal studies. At the ACC meetings, the French group, led by Dr. Cribier, also provided a further update on the current status of the initial six patients in whom this type of device was implanted. All of the patients were not considered surgical candidates. Because of the large size of the sheath and device catheter (24-F sheath), the transseptal approach has been used to avoid placing such a device into the arterial system. They reported one procedural death and noted one week after the procedure that the aortic valve area had increased from 0.57 to 1.67 cm^2, with an increase in the left ventricular ejection fraction (LVEF) from 24% to 39% in the five survivors (10). The era of percutaneous valve replacement seems under way, but still a long way from widespread clinical application.

From the surgical standpoint, Bhudia et al. (11) reported a retrospective series on the Cleveland Clinic's experience in operating on patients with severe aortic insufficiency (AI) and poor LV function (LVEF <30%). They separated their experience with this group (n = 88) into two time segments: 1972 to 1984 and 1985 to 1999. Hospital mortality before 1985 was as high as 50% in 1972, and progressively fell during the next 12 years. After 1985, they claim no operative deaths occurred (0 of 35). Rather remarkably, as well, they found no difference in the long-term (up to 10 years) survival curve between patients operated on after 1985, as compared with a matched cohort of patients with AI and an LVEF >30%. These data suggest that there may be no level of measurable LV dysfunction below which aortic valve surgery for AI should be withheld.

There also continues to be interest in the use of combined or "hybrid" procedures combining percutaneous coronary intervention (PCI) with subsequent valvular surgery. The group at the Brigham and Women's Hospital reported their experience from 1997 to 2003 with 26 such patients (12). All were hemodynamically unstable and considered high-risk valve/coronary artery bypass grafting (CABG) patients. All had angioplasty, and 22 (85%) of 26 had stenting. The

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patients subsequently went to the operating room a median of five days after PCI. Concomitant CABG was performed in 10 patients. Operative mortality was low (1 [3.8%] of 26), although five-year survival was 44%. It was not clear how many received ticlopidine or clopidogrel after the coronary stent procedure, and whether this would have blunted the enthusiasm for this approach. The data are provocative in suggesting that such hybrid procedures are at least feasible and apparently safe.

The puzzle as to why calcium deposits in heart valves over time was further investigated in a variety of abstracts. Kaden et al. (13), from Germany, for instance, extracted normal, sclerotic, and stenotic tricuspid aortic valves and, using a semi-quantitative immunostaining method, looked for the presence of C-reactive protein (CRP) within the valves. They found it absent in normal valves, present in sclerotic valves, and strongly present in stenotic valves. When cultured aortic valve myofibroblasts were then stimulated with CRP, they noted an increased expression of matrix metalloproteinase-1 (MMP-1). Others have reported an increase in MMP-1 in aortic stenosis (14). Matrix metalloproteins are proteolytic enzymes that lead to the degradation of the extracellular matrix; overexpression has been associated with a variety of processes, most notably osteoarthritis (15).

The relationship between rheumatic valve calcification and inflammation was investigated by the groups at the Mayo Clinic and Northwestern University (16). Extracted rheumatic heart valves were compared to normal human valves. The valves were studied by a variety of methods, including micro-computed tomography, hematoxylin-eosin staining, and Masson's trichrome staining for anatomic features. Immunohistochemistry was used to localize osteopontin protein, alpha-actin, and CD34. Stains were also made for vascular endothelial growth factor (VEGF), von Willebrand factor, and human macrophages (CD68). The bottom-line finding from the studies was that calcification was observed in mineralized tissue, with VEGF and CD34 appearing in areas of inflammation. New vessel formation was only found in the rheumatic valvular tissue. Inflammatory markers were much more evident in the rheumatic valves and were minimally present in normal valves. The authors' conclusions suggest a possible mechanism for the ongoing rheumatic process in these affected valves. These observations appear to confirm that angiogenesis and ongoing osteoblastic bone formation are active and ongoing processes in rheumatic heart valve tissue.

The first results from the newly organized prospective International Endocarditis Database were also presented by Cabell et al. (17). Thirty-four centers in 15 countries participated, and 1,024 cases from January 2000 to November 15, 2002 were available for review. Some of the initial observations include the fact that preceding dental procedures are now less common (7.9%) than other invasive procedures (18.7%). Of interest, *Staphylococcus aureus* (32.4%) now leads all other organisms as the cause of endocarditis, including infection from *Streptococcus viridans* (13.1%) and *Enterococcus faecalis* (10.6%). Surgery is required for 45.2% during the acute episode. Complications are frequent, with embolic events (stroke 16.7%, other emboli 22.7%), heart failure (31.3%), and intracardiac abscess (16.2%) leading the way. Even in an era of enhanced diagnostic tools and antibiotics, death still occurred in a disappointingly high percentage (19.4%). The univariate predictors of a fatal outcome include age, diabetes, hemodialysis, long-term indwelling catheters, stroke, congestive heart failure, and an intracardiac abscess. The most deadly organisms include coagulase-negative staphylococci (26%), *Staphylococcus aureus* (24.2%), and enterococci (21.1%). This data base provides a sobering look at endocarditis in the modern era. It will be an invaluable resource for making improvements in our diagnosis and treatment regimens of this devastating disorder.

Finally, an interesting echocardiographic and homodynamic feature was presented by Vaturi et al. (18). In patients with pulmonary hypertension, the authors observed a greater degree of TR when LV dysfunction was present. When the tricuspid apparatus was examined in greater detail, they observed bulging of the interventricular septum toward the right ventricle in patients with LV dysfunction, resulting in displacement of the tricuspid chordae and abnormal tricuspid leaflet tethering. The abnormal tethering allowed for superior buckling of the anterior leaflet and restriction of the septal leaflet. This consequence was the production of an eccentric tricuspid jet and more TR. In fact, an eccentric TR jet was impressively more evident in the LV dysfunction patients compared with those with normal LV function (68% vs. 7%, $p < 0.001$).

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